



Synthesis of New Medium- and Large- Sized Racemic and Chiral Lactones

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Abstract: Successive reaction of long chain ω -1, ω -2, ω -4 and ω -5 hydroxycarboxylic acids **1a-1e** with a cyanuric chloride (CC) and triethylamine afforded the corresponding racemic lactones **2a-2e** in high yields. Optically pure *R* lactones **4a-4e** were synthesized stereoselectively by porcine pancreas lipase-catalyzed resolution of racemic **2a-2e**. The resolution conditions were investigated, determined and optical rotations were measured. The mentioned chiral lactones were synthesized by this method for the first time. The obtained racemic and chiral lactones were analyzed by NMR, IR, Mass, optical rotation, and elemental analysis.

Keywords: Synthesis, medium and large ring, lactone, enzymatic resolution

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INTRODUCTION

Racemic and chiral lactones are commonly found in natural products as a series of pheromones and medical compounds (1-9). They are used also as intermediates for the synthesis of biological substances and natural products (10) due to their biological activities. There are many types of lactones and among them alkyl substituted lactones have gained a lot of interest from the synthetic and medicinal chemists (11, 12). Short chain alkyl lactones are essential and significant aromatic compounds in beverages and food.

Enzymes as biocatalysts find significant usage for preparing enantiomerically pure compounds (13). Lipases (triacylglycerol hydrolases, EC 3.1.1.3) are the most commonly used enzymes. They are not only cheap and easy to deliver but also are highly stable and have high enantioselectivity in synthesis.

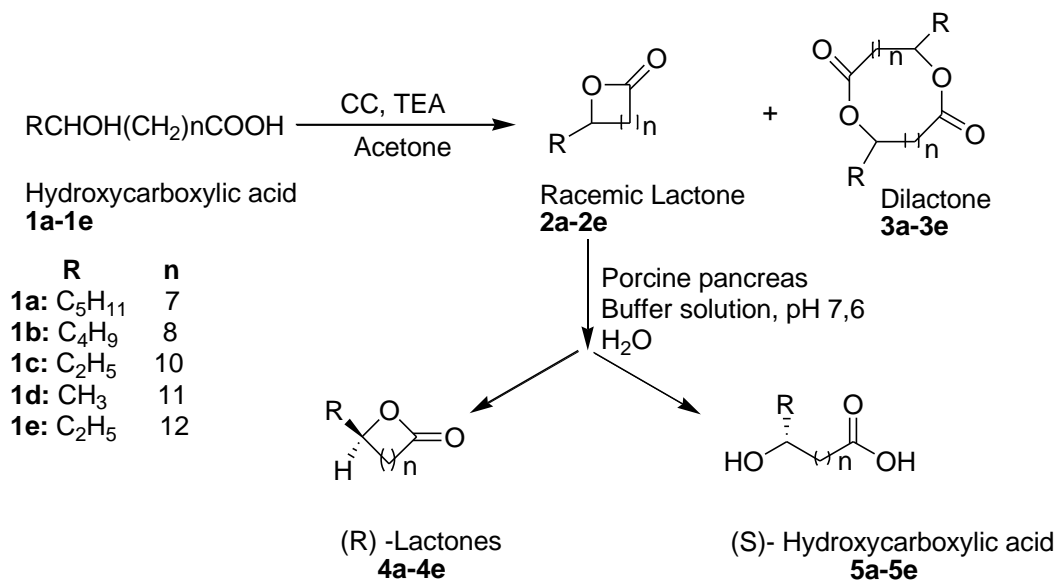
Various synthetic procedures have been declared in the literature for the preparation of racemic and enantiomerically pure medium and large- ring sized lactones. Several methods using reagents like DCC (14), 2,4,6-trichlorobenzoyl chloride (15), 2,2'-dipyridyl disulfide /Ph₃P (16), 1-methyl-2-chloropyridinium iodide / Et₃N (17), 2-Me-6-NO₂-benzoic anhydride (18,19) and cyanuric chloride (20) have been known for the preparation of the lactones from their corresponding hydroxy acids.

Cyanuric chloride method was chosen in this study, because it is an economical and commercially available reagent. This method has been applied for the synthesis of isoambrettolide (20), exaltolide (21), phorocantholide (21,22), pentadecanolide (22) and patutolide (23). According to the literature survey, the synthesized racemic lactones **2a-2e** have not yet been synthesized by cyanuric chloride method. The obtained *R*- lactones **4a-4e** were synthesized by hydrolysis of porcine pancreatic lipase by the first time in this work.

Racemic forms of 12-tetradecanolide (**2c**) and 14-hexadecanolide (**2e**) were obtained before differently from the used method in this study (24). There is no record available about their enantiomeric forms **4c** and **4e**. Information on racemic and chiral 9-tetradecanolide (**2a**) and 13-tetradecanolide (**2d**) is accessible (25-29), but the procedures are not the same. Racemic forms of **2a**, **2c**, **2d** and **2e** were found in the literature but the methods are dissimilar. Chiral **4a**, **4c**, **4d** and **4e** were known compounds but their preparation methods are not similar. Racemic 10 tetradecanolide (**2b**) and chiral (**4b**) are original compounds in this study.

These synthesized racemic and chiral lactones can be used in perfumery, medicine, and chemistry as ionic liquids and chromatographic separators due to their ring size. In previous studies, lactones and their derivatives were used as elastase inhibitors (30, 31), but this

inhibition was carried out there only with small ring lactones. In the future, these mentioned racemic and chiral lactones **2a-2e**, **4a-4e** will be examined for their inhibition of different enzymes especially for their elastase activity, which plays an important and protective role against diseases of lung, arteries, skin, and ligaments.



Scheme 1. Synthesis of medium and large sized racemic and enantiomeric lactones.

EXPERIMENTAL SECTION

General

All reagents were purchased from commercial products and were used without further purification. Acetone and triethylamine were dried with CaCl₂. The reactions were followed up with TLC plate (Merck 60 F-254). Column chromatography was performed on silica gel 60 (70-230 mesh). ¹H-NMR and ¹³C-NMR spectra were moderated in CDCl₃ and booked on a Varian (400 MHz). Mass spectra (ESI) were recorded on a Thermo Finnigan Spectrometer. Infrared (IR) spectra were booked on a Mattson 1000 series spectrometer as thin films between NaCl plates. Optical rotations were measured on an Optical Activity AA-55 digital polarimeter.

General method for the synthesis of chiral lactones

Enzymatic hydrolysis of substrate / PPL of varying the weight ratio and reaction time (entries 1-4) were applied by the conditions described in Table 3. Several suspension amounts of the racemic lactones (2a-e, 100 mg) were incubated at pH 7.6 (citric acid/Na₂HPO₄ buffer solution 0.02 M) and 36 °C in water. The obtained suspension was stirred in an ultrasonic bath. Then, the reaction was finished with the supplementation of CH₂Cl₂ (32) at the time shown in the Table III. The organic layer was separated, washed with distilled water and dried with Na₂SO₄. The solvent was removed *in vacuo*. To offer a mixture (R)-4a-e and (S)-5a-e that was separated with column chromatography (silica gel, hexane/ethyl acetate= 4/1 v:v) to give

lactones in good yield. The obtained lactones that are not UV-active can be seen by the TLC plate dipped into a 5% H₂SO₄ solution and then heated.

(9*R*)-(-)-9-tetradecanolide (**4a**). 58% yield (58 mg) as a colorless oil, hexane/ethyl acetate=4/1 R_f: 0.44. $[\alpha]_D^{20} = -28^\circ$ (c 0.45, CHCl₃). FTFTIR (neat): $\nu_{\max} = 2946, 2865, 1727, 1188 \text{ cm}^{-1}$. ¹H-NMR (400 MHz, CDCl₃): $\delta = 0.84$ (t, *J* = 7.3 Hz, 3H), 0.98-1.1 (m, 2H), 1.2-1.33 (m, 14H), 1.46-1.7 (m, 4H), 2.27 (ddd, *J* = 14.16, 7.8 and 5.3 Hz, 2H), 4.82 (m, 1H) ppm. ¹³C-NMR (125 MHz, CDCl₃): $\delta = 9.9, 22.2, 24.6, 26.4, 28.1, 28.4, 28.6, 28.7, 28.9, 32.6, 34.00, 40.2, 74.00, 172.75$ ppm. MS (EI): *m/e* 227 [M+1]⁺. Anal. Calc. for C₁₄H₂₆O₂: C, 74.29; H, 11.58. Found: C, 74.20; H, 11.52.

(10*R*)-(-)-10-tetradecanolide (**4b**). 54% yield (54 mg) as a colorless oil, hexane/ethyl acetate=4/1 R_f: 0.41 $[\alpha]_D^{20} = -25^\circ$ (c 0.45, CHCl₃). FTIR (neat): $\nu_{\max} = 2919, 2865, 1730, 1212 \text{ cm}^{-1}$. ¹H-NMR (400 MHz, CDCl₃): $\delta = 0.89$ (t, *J* = 6.8 Hz, 3H), 1.18-1.32 (m, 14H), 1.42-1.7 (m, 6H), 2.25 (m, 2H), 4.88 (dddd, *J* = 7.8, 6.8, 6.35 and 3.9 Hz, 1H) ppm. ¹³C-NMR (125 MHz, CDCl₃): $\delta = 12.95, 21.59, 24.12, 24.28, 26.53, 27.66, 27.97, 28.11, 28.30, 32.85, 33.69, 34.12, 76.11, 175.26$ ppm. MS (EI): *m/e* 227 [M+1]⁺. Anal. Calc. for C₁₄H₂₆O₂: C, 74.29; H, 11.58. Found: C, 74.25; H, 11.52.

(12*R*)-(-)-12-tetradecanolide (**4c**). 50% yield (50 mg) as a colorless oil, hexane/ethyl acetate=4/1 R_f: 0.32. $[\alpha]_D^{20} = -26^\circ$ (c 0.45, CHCl₃). FTFTIR (neat): $\nu_{\max} = 2920, 2865, 1728, 1202 \text{ cm}^{-1}$. ¹H-NMR (400 MHz, CDCl₃): $\delta = 0.84$ (t, *J* = 7.3 Hz, 3H), 0.98-1.1 (m, 2H), 1.2-1.33 (m, 14H), 1.46-1.7 (m, 4H), 2.27 (ddd, *J* = 14.16, 7.8 and 5.3 Hz, 2H), 4.82 (m, 1H) ppm. ¹³C-NMR (125 MHz, CDCl₃): $\delta = 9.99, 24.2, 24.6, 26.4, 28.1, 28.4, 28.6, 28.7, 28.9, 32.6, 34.00, 40.2, 74.00, 172.75$ ppm. MS (EI): *m/e* 227 [M+1]⁺. Anal. Calc. for C₁₆H₂₆O₂: C, 74.29; H, 11.58. Found: C, 74.27; H, 11.56.

(13*R*)-(-)-13-tetradecanolide (**4d**). 60% yield (60 mg) as a colorless oil, hexane/ethyl acetate=4/1 R_f: 0.27. $[\alpha]_D^{20} = -33^\circ$ (c 0.45, CHCl₃). FTIR (neat): $\nu_{\max} = 2919, 2865, 1728, 1266, 1104 \text{ cm}^{-1}$. ¹H-NMR (400 MHz, CDCl₃): $\delta = 1.19$ (d, *J* = 6.25 Hz, 3H), 1.22-1.51 (m, 16H), 1.54-1.64 (m, 2H), 1.66-1.72 (m, 1H), 1.94-2.05 (m, 1H), 2.26 (ddd, *J* = 15.09, 7.5 and 4.3 Hz, 1H), 2.34 (ddd, *J* = 15.09, 7.4 and 4.3 Hz, 1H), 4.9 (qdd, *J* = 6.76, 12.25 and 6.25 Hz, 1H) ppm. ¹³C-NMR (125 MHz, CDCl₃): $\delta = 14.49, 23.73, 25.23, 25.99, 29.38, 29.49, 29.78, 29.87, 34.65, 39.63, 39.65, 60.39, 68.44, 174.17$ ppm. MS (EI): *m/e* 227 [M+1]⁺. Anal. Calc. for C₁₄H₂₆O₂: C, 74.29; H, 11.58. Found: C, 74.26; H, 11.52.

(14*R*)-(-)-14-hexadecanolide (**4e**). 56% yield (56 mg) as a colorless oil, hexane/ethyl acetate=4/1 R_f: 0.25. $[\alpha]_D^{20} = -44^\circ$ (c 0.45, CHCl₃). FTIR (neat): $\nu_{\max} = 2919, 2865, 1732, 1185 \text{ cm}^{-1}$. ¹H-NMR (400 MHz, CDCl₃): $\delta = 0.86$ (t, *J* = 7.3 Hz, 3H), 1.1 (m, 2H), 1.2-1.34 (m, 16H),

1.48-1.62 (m, 6H), 2.28 (ddd, $J= 14.65, 7.8$ and 4.3 Hz, 2H), 4.8 (m, 1H) ppm. ^{13}C -NMR (125 MHz, CDCl_3): $\delta= 8.7, 24.34, 24.42, 25.26, 25.95, 26.24, 26.76, 27.95, 28.12, 28.54, 30.48, 32.62, 33.74, 37.10, 74.15, 175.26$ ppm. MS (EI): m/e 254 $[\text{M}]^+$. Anal. Calc. for $\text{C}_{16}\text{H}_{30}\text{O}_2$: C, 75.53; H, 11.89. Found: C, 75.48; H, 11.85.

General method for the synthesis of racemic lactones

0.01 mole of hydroxy acid was placed in a two-necked reaction flask equipped with a magnetic stirrer. It was dissolved in 100 mL of acetone with heating (if necessary) and cooled to room temperature. 0.01 mole of cyanuric chloride and 0.02 mole of triethylamine was added until a clear solution was obtained. After about 20 minutes, a precipitate comes out and gradually increases. The obtained precipitate was filtered. The filtrate was diluted with water and extracted with chloroform. The organic phase was washed with 10% Na_2CO_3 and water, dried by Na_2SO_4 , and evaporated. The colorless oil was purified by flash chromatography to give lactones in excellent yield (20).

9-tetradecanolide (**2a**). This compound is a colorless oil and has 64% yield. The spectroscopic data were identical to that of enantiomeric **4a**.

10-tetradecanolide (**2b**). This compound is a colorless oil and has 73% yield. The spectroscopic data were identical to that of enantiomeric **4b**.

12-tetradecanolide (**2c**). This compound is a colorless oil and has 75% yield. The spectroscopic data were identical to that of enantiomeric **4c**.

13-tetradecanolide (**2d**). This compound is a colorless oil and has 78% yield. The spectroscopic data were identical to that of enantiomeric **4d**.

14-hexadecanolide (**2e**). This compound is a colorless oil and has 54% yield. The spectroscopic data were identical to that of enantiomeric **4e**.

RESULTS AND DISCUSSION

The starting substances 9-, 10-, 12- hydroxytetradecanoic acids and 14-hydroxyhexadecanoic acid (**1a-1e**) were synthesized by NaBH_4 reduction and hydrolysis of their corresponding keto esters, which were prepared by Blaise condensation method (33) and 13-hydroxytetradecanoic acid was obtained according to the acetoacetic ester method with good yields (Table 1) (34, 35).

Table 1: The results of synthesized racemic hydroxy acids (RHOHC(CH₂)_nCOOH (**1a-1e**)).

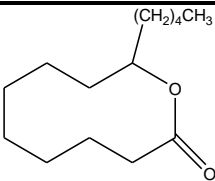
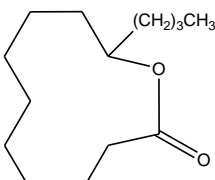
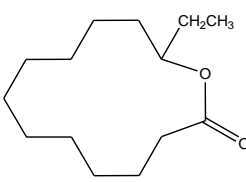
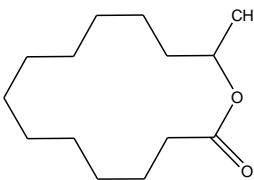
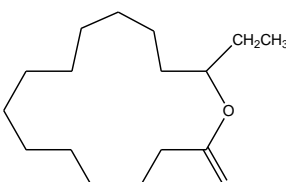
Entry	R	n	Hydroxy Acids	mp (°C)	n_D^{80}	Yield %	*
1	C ₅ H ₁₁	7	1a	69-70	1.4432	80	
2	C ₄ H ₉	8	1b	57-58	1.4410	85	
3	C ₂ H ₅	10	1c	58-59	1.4390	90	
4	CH ₃	11	1d	58-59	1.4405	90	
5	C ₂ H ₅	12	1e	59-60	1.4420	95	

* Isolated yield.

The synthesized hydroxycarboxylic acids were converted to their corresponding racemic lactones by cyanuric chloride method (Scheme 1, Table 2).

The best lactonization yield was found for the molar fraction of hydroxy acid:CC:TEA as 1:1:2. Increased ring size is reduced the efficiency of lactonization yield (Table 2, entries 13-15). The size of alkyl substitution has not played an important role in the lactonization yield. Various acetone amounts were tried to increase of the lactonization reaction yield, the optimal amount was found to be 10 mL (Table 2). The lactonization was carried out at room temperature until the disappearance of hydroxy acid. The reaction was also examined at refluxing temperature for the reduced reaction time, but dilactone was obtained as a by-product in this reaction. Therefore, lactonization was preferred at room temperature. (Table 2).

Table 2: Synthesis of medium- and large-sized racemic lactones.

Entry	R	n	Lactone	Acetone (mL)	Yield (%) ^[b]
1		7	2a	10	65 (19 ^[c])
2				20	64 (20 ^[c])
3				30	63 (18 ^[c])
4		8	2b	10	74.5 (10 ^[c])
5				20	73 (11 ^[c])
6				30	72 (12 ^[c])
7		10	2c	10	76 (17 ^[c])
8				20	75 (18 ^[c])
9				30	74 (19 ^[c])
10		11	2d	10	80 (21 ^[c])
11				20	78 (20 ^[c])
12				30	78.5 (19 ^[c])
13		12	2e	10	56 (9 ^[c])
14				20	54 (10 ^[c])
15				30	53 (11 ^[c])

[a] Conditions, hydroxycarboxylic acids 1 mmol, cyanuric chloride (CC) 1 mmol, triethylamine (TEA) 2 mmol, t= room temperature, reaction time: 24 h. [b] Isolated yield. [c] Dilactone yield.

Choice of lipase enzyme to be used

According to the literature survey made, porcine pancreas lipase was considered to be proper in the enzymes for enzymatic hydrolysis. Moreover, it is advantageous that this enzyme is much more economical than other enzymes. It hydrolyzed the *S* enantiomers making the formations of (*R*)-**4a-4e** by enzyme PPL chosen in this study. The best conditions for synthesis of (*R*)-**4a-4e** in good yields are given in Table 4.

Table 3: Enantioselective resolution of **2a-2e** by PPL.

Entry	<i>(R)</i> - 4a		<i>(R)</i> - 4b		<i>(R)</i> - 4c		<i>(R)</i> - 4d		<i>(R)</i> - 4e	
	$[\alpha]_D^{20}$	Yield ^a	$[\alpha]_D^{20}$	Yield ^a	$[\alpha]_D^{20}$	Yield ^a	$[\alpha]_D^{20}$	Yield ^a	$[\alpha]_D^{20}$	Yield ^a
		%		%		%		%		%
1	-27°	45	-22°	35	-25°	38	-30°	42	-39°	41
2	-28°	58	-25°	54	-26°	50	-33°	60	-44°	56
3	-20°	20	-21°	25	-23°	30	-29°	34	-36°	36
4	-19°	10	-20°	20	-24°	25	-28°	30	-31°	32

^a isolated yields

Table 4: PPL-catalyzed hydrolysis of racemic **2a-2e** with different ratios of substrate/PPL.

Entry	Substrate ^a (mg)/ Suspension ^b (cm ³)	PPL (mg)/ Suspension(cm ³)	Substrate/PPL	Reaction time(h)
1	1,000:56	1,000/56	1:1	7
2	1,000:28	500/28	2:1	7
3	1,000:18.67	333:18.67	3:1	7
4	1,000:9.33	166.6:9.33	6:1	7

^a Racemic 2a-e (1.000 mg) was taken in these procedures.

^b 1 cm³ of suspension, produced from 1 g of lipase and 15 cm³ of water, hydrolyzed 50 mg of trimyristine (36)

The best resolution for **2a-2e** was entry 3. *(R)*-**4a-4e** were synthesized with good yields after 7 h incubation with a substrate/PPL weight ratio 2:1 (Entry 2, Table 4). There are a lot of studies mentioned about chiral lactones that clearly refined by R configuration due to negative optical rotation. Therefore, the synthesized chiral lactones were attributed to be of R configuration according to the measured optical rotations. The configurations of the chiral lactones with negative sign were defined in the literature as *(R)* (25-29).

Therefore, enantioseparation studies were also tried in this work and the enantiospecificity of the resolution was determined after purification of the *(R)*-**4a-4e** by column chromatography. For determination of enantiomeric enrichment (% ee), Cyclodex β-25 m column chiral capillary GC column was used for gas chromatographic separation. Different GC separation conditions were tried, but resolution of *(R)* and *(S)* enantiomers of the obtained lactones were not succeeded. Configuration of the synthesized lactones were assigned due to the optical rotation degrees in the literature (24-28), where lactones with negative optical rotations were defined as *(R)*. Therefore the synthesized lactones in this study were attributed to be of R configuration (Table 3). Synthesized racemic and chiral lactones were obtained for the first time by the method used in this study.

CONCLUSION

In this work, medium- and large-ring racemic **2a-2e** and chiral lactones **4a-4e** were synthesized in good yields. The enzymatic resolution of the synthesized racemic lactones was carried out under mild conditions. The described processes in this study are cheap and environmentally friendly. The purification of the lactones were achieved by column chromatography. The synthesized racemic and chiral lactones **2a-2e** and **4a-4e** mentioned were analyzed by FTIR, ¹H-NMR, ¹³C-NMR, Mass spectra, optical rotation, and C,H analysis. The synthesized racemic and chiral lactones will be examined in the future for their usefulness in food, pharmacy and cosmetic industries. They will be investigated for their inhibition effect of several enzyme types.

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